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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/461,652	06/05/95	KWON	P IND4-P11

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EXAMINER	
KAUFMAN,C	
ART UNIT	PAPER NUMBER
1812	10

DATE MAILED: 07/22/97

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 5/2/97

☑ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 5, 6, 20, 21, 24-26 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 5, 6, 20, 21, 24-26 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

DETAILED ACTION

1. The amendment filed 5/2/97 has been entered.

2. ***Response to Arguments***

The rejection of claim 6 under 35 USC 101 is withdrawn in view of the amendment to the claim.

The rejection of claims 21, 22, and 24-26 under 35 USC 112, second paragraph is withdrawn in view of the amendments to the claims.

Applicant's arguments filed 4/30/97 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. ***Priority***

Applicant's claim for priority is acknowledged. However, the parent applications 07/922,996 and 08/012,269 did not provide adequate support under 35 U.S.C. 112 for claims 5, 6, 21, 22, or 24-26 of this application. Support is lacking in that there is not adequate written description. Even if both the cDNA and amino acid sequences of H4-1BB, called "PLD78" was present in the earliest priority application (07/267,577), intervening applications did not contain that sequence and the current application when filed did not incorporate by reference that earliest parent application, so that continuity was not maintained (see MPEP 608.01(p)). Those applications did not teach the human H4-1BB with sufficient description (*i.e.*, amino acid or nucleic acid structure, or a deposited plasmid containing the encoding DNA) to enable it. Only the suggestion of isolating a human protein corresponding to mouse cDNA 4-1BB is present. The two most recent prior applications provided only an invitation to experiment. This situation

is analogous to that decided by the court in *Amgen Inc v. Chugai Pharmaceuticals Co. Ltd.*, 18 USPQ2d, 1016 (CAFC 1991) where at issue was a claim to a nucleic acid molecule encoding human erythropoietin (EPO) with no direct structural characteristics disclosed. The court stated that:

> A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See *Oka*, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when and inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.

While Applicants had a method of obtaining the H4-1BB gene, the parent application did not have a detailed constitution of the gene to distinguish it from other materials. For the reason above, the parent application is not enabling for H4-1BB or fragments thereof.

Sequence in Claims

4. 37 CFR 1.821(d) requires the use of an assigned sequence identifier in all instances where the description or claims of a patent application discuss a sequence regardless of whether a given sequence is also embedded in the text of the description or claims of an application. See MPEP 2422.03. The sequence shown in Claim 21 does not constitute new matter because it is shown in SEQ ID NO:2 in the paper copy of the "Sequence Listing". The amino acids shown in claim 21 can be identified in one of two ways: First, the claim can be amended so that a phrase to the effect of "amino acid positions 24-35 of SEQ ID NO:2" is added to the claim; or a unique sequence identifier may be assigned to that peptide and

substitute copy of the CRF and paper "Sequence Listing" may be submitted with a statement declaring that no new matter has been introduced by the new sequence and that the CRF and paper copies are the same.

5. ***Claim Rejections - 35 USC § 112, First Paragraph***

The rejection of claims 21, 24, and 25-26 under 35 U.S.C. 112, first paragraph, are maintained for the reason of record in paragraphs 4b, 4d, and 4e, respectively, in the previous Office action filed 4/19/96 (paper no. 4). For the rejection of claims 25 and 26 put forth in paper no. 4, deletion of the term "an effective amount" by the amendment filed 11/22/96 obviates only the related part of the rejection of record. Applicant's response to this rejection was answered by the Examiner in the Office action mailed 2/3/97 (paper no. 7) in section 10.

Claim 5 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full-length receptor having SEQ ID NO: 2, does not reasonably provide enablement for another receptor/polypeptide produced from cDNAs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims for the reason of record in section 11 of the previous Office action filed 2/3/97 (paper no. 7).

Claim 21 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full-length protein of SEQ ID NO:2, does not reasonably provide enablement for fragments of that protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reason of record in section 12 of the previous Office action filed 2/3/97 (paper no. 7).

Claims 22 and 24 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide having the full-length sequence of SEQ ID NO:2, does not reasonably provide enablement for fragments thereof. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reason of record in section 13 of the previous Office action filed 2/3/97 (paper no. 7).

Claims 25 and 26 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention for the reason of record in section 14 of the previous Office action filed 2/3/97 (paper no. 7).

In Applicant's response each rejection was not addressed individually, but instead were taken as a group, and will be addressed as a group in this paper.

Applicant argues (p. 5-6) that, " The important point is that the relevant prior art acts in a complementary fashion to the disclosure itself.... Here the specification, and the incorporated art and artisans, teach how to use a the H4-1BB sequence, once it is known as such." This is agreed with. However, in the current situation, only H4-1BB having the DNA and amino acid sequence of SEQ ID NO: 1 and 2, respectively, are disclosed. No other "H4-1BB" sequences are disclosed. Additionally, which amino acids formed the extracellular domain are not specified and the specification does not provide support for a fragment of H4-1BB consisting of amino acids 24-186, for example. The point of non-enablement of the fragments is that there is insufficient written description in the specification to lead one to those specific amino acids--no functional or structural characteristic specifically associated with anything but the full-length protein having SEQ ID NO:2 or the protein comprising amino acids 24-255 of SEQ ID NO:2.

Applicant argues (p. 6) that with the knowledge of the relevant technology provided by a host of sources of art including 3 relevant textbooks cited in Applicant's response, all before the proposed 1988 priority date, a given discovery would not only provide a litany of potential uses, but would indicate what techniques and steps would be useful to make a more complete use of the discovered technology. If it were true that the references provided enablement in connection with

the suggestion of the existence of a compound, then those references along with the suggestion would make the current invention obvious. This would constitute defining a compound without knowing its structure and only a hoped for function or homology. The courts have held that is not sufficient to define actual conception of a compound (see for example *Amgen Inc. v. Chugai*... cited above).

Applicant argues (p. 6) that "With regard to the nature of the specification in the instant matter, the uses or technological steps necessary to make the invention disclosed by the Applicant need not be apparent to everyone, *all that is required* is that enablement, and the potential usefulness of the disclosure is communicated to the skilled artisans of the relevant technology, here the use of known amino acid sequence bearing more than substantial homology to the mouse 4-1BB and belonging to the superfamily of nerve growth factors.... The point is that the disclosure of the Applicant, and those citations disclosing the state of the art are sufficient to demonstrate that H4-1BB ... can support the relevant claims." This argument has been fully considered, but is not persuasive. The showing of a method of obtaining a product and potential uses of the unmade product do not provide enablement for an invention. They serve only to define the protein by its hoped-for-function. This case is analogous to that reviewed by the courts in *Fiers v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993) cited below. The court said that conception does not occur until the invention can be described with particularity. A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date, In re Glass, 492 F.2d 1228; 181 USPQ 31 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention.

Applicant argues (p. 7) that applying the Wands standards, the claimed invention would not require undue experimentation to practice. This argument has been fully considered, but is

not persuasive. As was stated in the previous Office action, according to the standards the court held in *In re Wands*, enablement of the current invention is not commensurate in scope with the claims because there is a lack of guidance in the specification relating to the structure H4-1BB that is necessary to know where the extracellular domain is and what functional properties fragments of H4-1BB posses; a lack of description of variants or proteins with modifications that have some sequence similarity with SEQ ID NO:2 which are encompassed by the name "H4-1BB" when it is not defined by sequence (see e.g., claim 5 and 21); the lack of description of the role of the mouse 4-1BB at the time the current application was filed and the relatively low sequence similarity of 65% between mouse and human 4-1BB; a lack of either direction or examples of killing cancer cells, treating autoimmune disease, or blocking immune response during organ transplantation that are pertinent to claims 25 and 26 which are drawn to pharmaceutical compositions; a lack of predictability due to that fact that even though H4-1BB is a member of the nerve growth factor superfamily, this superfamily contains a variety of receptors with different structures (especially in the extracellular domain) as shown in Carpenter (W); the breadth of the claims 5, 21, 25, and 26 as they relate to the "H4-1BB" without sufficient description of structure and of claims 22 and 24 without sufficient description of structure in the specification to lead one skilled in the art to those fragments; and, even assuming a high level of skill in the prior art, for the reasons listed above, it would indeed require undue--not routine--experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 103

6. Claims 5, 6, 21, 22, and 24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Schwarz et al. (U) in view of Ayala et al. (V).

Applicant argues that The GenBank reference of Schwarz et al. is not a "publication", but that such GenBank submissions "are simply the deposit of lists of putative amino acid sequences that themselves have little or no meaning." This argument has been fully considered, but is not

persuasive. Contrary to Applicant's assertion that "these lists are impenetrable unless you already known what you are looking for", GenBank is designed so that both sequences and words can be searched for. A person of ordinary skill in the molecular biology art would have been readily familiar with GenBank, and methods of accessing and searching the information contained therein, as well as the database's great value as a research tool for elucidation of potential homology and function which are properties of a novel chain of amino acids. This database was open to and used by the public because of such advantages.

Applicant further argues that to suggest that a GenBank deposit by itself has significance with regard to publication or prior disclosure recognized under 35 USC 103, is to suggest that the bare filing of randomly generated amino acid sequences would bar the novelty of later discovered genes, with known functions, utilities and applications to real world concerns. Note first that full function of the currently claimed invention is not know and its use in a pharmaceutical composition is not enabled as stated above. In a related argument, Applicant says that if only bare amino acid sequences, without more (e.g., identify, function , cDNA, or any knowledge or a homologue/analogue) is considered enabling, then the previously filed applications are also enabling. This is agreed with, however, the reference relied upon provides much more than a bare sequence. The GenBank record of the compound of Schwarz et al. describes not only the mRNA and deduced amino acid sequence, but also the fact that it was a human activation dependent T cell mRNA (definition section), it was a cell surface receptor (keywords section), and the title says that it was a member of the nerve growth factor receptor and tumor necrosis factor receptor family. The disclosure was public as stated in the previous Office action in the paragraph bridging pages 11 and 12. One skilled in the art would known the advantage of using the public GenBank database.

Applicant also argues that the previous applications in light of the prior art are enabling. This argument has been fully considered, but is not persuasive. The prior application (08/122,796) did not disclose the DNA or amino acid sequence of H4-1BB. The prior art of

Schwarz et al. did disclose an amino acid sequence which was 99.8% identical to the claimed invention and was encoded by a single nucleic acid sequence. The prior application provided only a mouse 4-1BB protein and nucleic acid sequence with the suggestion of how to obtain a human homologue of the protein, yet had no description of the human homologue sufficient to distinguish it from other compounds and, therefore, had a lack of adequate written description.

Applicant argues that "the art **must** at least indicate that a combination [of specific features] would be possible and desirable in order to render a future combination of that art obvious to one skilled in the relevant field of art." This argument has been fully considered, but is not persuasive. The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. In re Fine , 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones , 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also In re Eli Lilly & Co ., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); In re Nilssen , 851 F.2d 1401, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); Ex parte Clapp , 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and Ex parte Levengood , 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning). (See MPEP 2144) It is believed that the Examiner has provided a convincing line of reasoning supporting the rejection based on logic and sound scientific reasoning.

Applicant argues that based on the court decision in *In re Bell* and *In re Beers* that the claimed product was not obvious. This argument has been fully considered, but is not persuasive. In the cited court cases only the amino acids sequence was known and, because of DNA sequence codon degeneracy, the actual structure/sequence of the encoding nucleic acid was not obvious. The current situation is distinguished from those cases because in this instance, a nucleic acid

sequence was in the prior art and a nucleic acid sequence can encode only a single protein sequence, even though one protein sequence can be encoded by a multitude of nucleic acid sequences.

7. *Conclusion*

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached at (703) 308-2957.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**stephen.walsh@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the

Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

cmk
July 20, 1997

Stephen Walsh
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SUPERVISORY PATENT EXAMINER
GROUP 1800